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Thyrotoxicosis

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KEYWORDS

• Hyperthyroidism • Thyroglobulin • TSH • Thyrotoxicosis • Endocrine emergency • Thyroid storm

KEY POINTS

- Patients with hyperthyroidism present with a myriad of signs and symptoms, with the most severe form, thyroid storm, resulting in severe end-organ injury.
- Management of subclinical hyperthyroidism and thyrotoxicosis without thyroid storm is tailored to the underlying cause. Patients generally benefit from thioamide therapy and outpatient management.
- Patients with thyroid storm require emergent treatment and resuscitation, including diagnosing and managing the underlying trigger (eg, antibiotics for infection); administering thionamides, steroids, and iodine; and managing agitation and/or hyperthermia.

INTRODUCTION

Terminology and Definition

Hyperthyroidism is defined as excess thyroid hormone activity and exists across a spectrum of disease severity ranging from subclinical hyperthyroidism to thyroid storm (**Fig. 1**). Subclinical hyperthyroidism is a condition wherein serum thyroid-stimulating hormone (TSH) is low or undetectable, but there are normal levels of thyroxine (T4) and total or free triiodothyronine (T3).[1] The prevalence of subclinical hyperthyroidism in the general population is estimated to approximate 0.7% to 2%.[2,3] Thyrotoxicosis is the inappropriate secretion of T4 and T3 and associated with the clinical manifestations of these elevated hormone levels, including weight loss, palpitations, tachycardia, and irritability.[2,3] Thyrotoxicosis may progress to thyroid storm, a condition with a mortality approaching 20%.[2–5] Although life-threatening, thyroid storm is a rare condition with an estimated incidence of 0.2 per 100,000 patient-years, affecting 0.22% of patients with thyrotoxicosis.[2,6]

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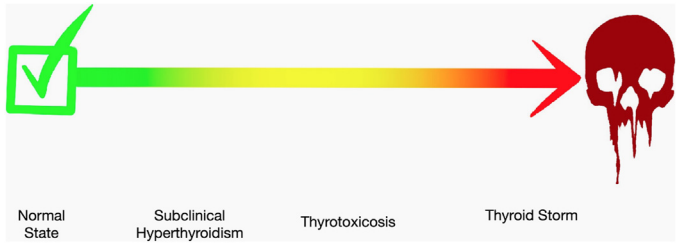

Fig. 1. Hyperthyroidism spectrum of severity.

PHYSIOLOGY

Within the hypothalamus, hypophysiotropic thyroid-releasing hormone (TRH) neurons provide stimulation to thyrotrophs of the anterior pituitary gland.[7–9] TRH stimulates the pituitary thyrotrophs to secrete TSH.[7,10] TSH acts on the TSH receptor with resultant effects on the thyroid gland.[11–13] These thyrocytes, in turn, produce iodothyronines and play important roles in the management of metabolism, protein synthesis, and iodine homeostasis.[8] Three iodothyronines are produced by the thyroid once signaled.[8,14] T4 is the main product of the thyroid and is largely inert, functioning as a prohormone until it is converted to T3, the active hormone.[8,14] Although small amounts of T3 are produced by the thyroid, most of the body's T3 comes from peripheral conversion of T4 by deiodinases (**Fig. 2**) in target organs of high blood flow, such as the liver and kidney (type 1 deiodinase), and within glial cells of the brain (type 2 deiodinases).[8–10,14]

Serum thyroid hormone then acts on the hypothalamus, inhibiting gene expression and also posttranslation processing of the prohormone (proTRH), creating the negative feedback loop of the HPT axis (**Fig. 3**).[7–9,14]

BACKGROUND, CAUSES, AND PATHOPHYSIOLOGY

There are numerous causes of thyroid hormone hyperactivity, resulting in both clinical and laboratory evidence of hyperthyroidism (**Box 1**).

Grave Disease

Grave disease (GD) is the most common cause of hyperthyroidism, with an incidence estimated at 20 to 50 per 100,000 patient-years and accounting for 60% to 80% of those with hyperthyroidism.[12,15–17] GD is the most common cause of thyrotoxicosis in patients developing thyroid storm.[18] Women are affected approximately twice as often as men, with a peak age of onset of 30 to 50 years.[12,19] GD is an autoimmune condition, resulting in the production of immunoglobulin G (IgG) that binds to TSH receptors, resulting in increased T4 and T3, as well as increased size and vascularity of the thyroid (**Fig. 4**).[3,4,12,15,17,18,20,21] Because of global thyroid stimulation, patients with this condition usually have diffuse, nontender, thyroid enlargement.[3]

Fig. 2. Conversion of T4 to T3.

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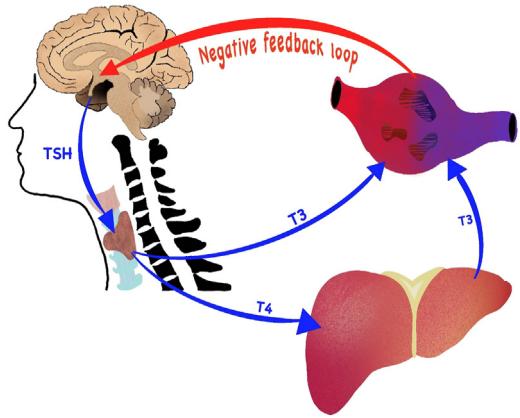

Fig. 3. Simplified hypothalamic-pituitary-thyroid axis.

Toxic Adenoma and Multinodular Goiter

Toxic adenoma, also called toxic nodular goiter, is a benign tumor of the thyroid gland that causes autonomous secretion of thyroid hormone.[3] Toxic multinodular goiter results from the formation of multiple autonomous benign tumors.[3] Symptoms typically progress in a stepwise fashion, beginning with subclinical hyperthyroidism and gradual progression to overt thyrotoxicosis if not treated.[3]

Thyroiditis

Subacute thyroiditis (SAT) or de Quervain thyroiditis is the most common cause of thyroid pain and generally is the result of a viral infection, although chemical or mechanical irritation and autoimmunity can precipitate SAT.[3,21–23] Patients typically present with nonspecific constitutional symptoms that may resemble an upper respiratory tract infection, followed by fever, severe anterior neck pain, and neck swelling.[3,21] Patients typically have elevated erythrocyte sedimentation rate and C-reactive protein levels.[3] Patients with SAT usually have a brief period of thyrotoxicosis lasting days to weeks, followed by a state of hypothyroidism and an eventual return to baseline.[3]

Box 1
Potential causes of thyrotoxicosis

Common causes:
- Grave disease
- Toxic adenoma and multinodular goiter
- Exogenous intake (thyrotoxicosis factitia)

Uncommon causes:
- Subacute thyroiditis
- Jod-Basedow phenomenon

Rare causes:
- TSH secreting pituitary adenoma
- Acute suppurative thyroiditis

Special considerations—gestational and gynecologic causes:
- Postpartum lymphocytic thyroiditis/painless lymphocytic thyroiditis
- Gestational transient thyrotoxicosis and gestational trophoblastic diseases
- Struma ovarii

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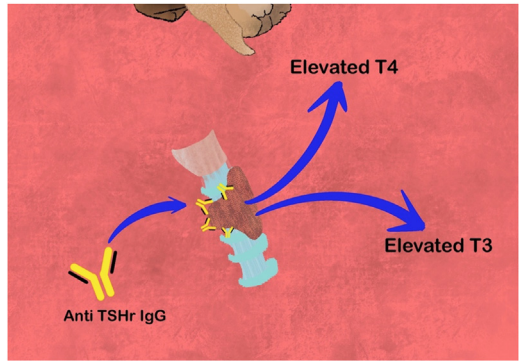

Fig. 4. Stimulation of TSH receptor (TSHr) by anti-TSHr IgG.

Acute suppurative thyroiditis (AST) is a rare but life-threatening cause of thyrotoxicosis.[21,23] AST is estimated to affect 0.1% to 0.7% of patients with thyroid disease and has a mortality between 3.7% and 9%.[23–26] Patients present with a similar constellation of symptoms as SAT, including anterior neck pain, fever, elevated inflammatory markers, and leukocytosis.[21,23–25] Up to 42% of patients will present with overt hyperthyroidism.[23] Diagnosis of AST is suggested in the presence of high fever or leukocytosis, overlying erythema, or suggestive imaging studies.[23]

Postpartum thyroiditis is potentially the best-characterized postnatal autoimmune thyroid disorder.[3,21,27] Although seen in the first year postpartum, it most commonly occurs 6 weeks to 6 months following delivery or pregnancy loss.[3,27] Postpartum thyroiditis affects up to 10% of postpartum women.[3] Postpartum thyroiditis occurs secondary to an autoimmune infiltration of lymphocytes and the subsequent release of thyroid hormone.[3] Postpartum thyroiditis is typically an exacerbation of a preexisting thyroid condition, and like SAT, has a biphasic clinical history with a period of thyrotoxicosis followed by hypothyroidism.[27]

EMERGENCY DEPARTMENT PRESENTATION

Hyperthyroidism presents clinically with a variety of signs and symptoms. Furthermore, there is often a precipitating event leading to the development of overt thyrotoxicosis (**Box 2**).

Box 2
Common factors precipitating overt thyrotoxicosis and thyroid storm[6,28]

- Irregular use of thyroid-suppressing medications
- Underlying infections
- Ischemia (myocardial, cerebral, limb, and mesenteric)
- Pregnancy
- Medication changes or noncompliance
- Diabetic ketoacidosis and other endocrinopathies
- Burns
- Trauma
- Overly aggressive palpation of the thyroid

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In most cases, thyrotoxic patients presenting to the emergency department (ED) with complaints of excessive thyroid hormone production or intake will demonstrate identifiable signs and symptoms, although these are often nonspecific.[18,28] Because of the variety of systems affected by thyroid hormones, there is a wide range of symptoms. **Table 1** demonstrates a list of commonly encountered symptoms.

Signs of thyrotoxicosis also vary and are represented in **Table 2**. Neuropsychiatric studies have shown a graded decline in memory and concentration proportional to the severity of thyrotoxicosis.[18,29] Because of increased estrogen, breast enlargement can occur in women, in addition to gynecomastia in men.[18,29] Spider angiomas and palmar erythema may also develop, possibly owing to increased estrogen or increased sex hormone-binding globulin.[29]

Elderly patients may not present with typical findings of thyrotoxicosis and instead present with apathetic thyrotoxicosis.[18] Apathetic thyrotoxicosis, also termed "hidden" or "masked" thyrotoxicosis, is marked by the cardinal features of apathy and depression.[18,30–34] This form of thyrotoxicosis is reported to affect the heart to a high degree, causing unexplained and often refractory heart failure or arrhythmias, including atrial fibrillation.[30]

Finally, patients may rarely present with a condition called thyrotoxic periodic paralysis (TPP). TPP classically presents with early morning muscle tightness and pain, which then progresses to brief paroxysms of bilateral lower-extremity paralysis.[29] The upper extremities may also be affected, although this is less common.[29] TPP is often associated with exercise, high carbohydrate intake, or insulin administration, with hypokalemia commonly discovered on laboratory evaluation.[29] Decreased TSH level helps distinguish TPP from hypokalemic periodic paralysis.

EVALUATION AND DIAGNOSIS

By virtue of the litany of signs, symptoms, and organ systems affected, diagnosis of thyrotoxicosis relies on the clinician considering the disease and obtaining a TSH sample.

Table 1
Symptoms of thyrotoxicosis[6,18,21]

Organ System	Symptom
Systemic	Heat intolerance Weight loss despite normal intake
Neuropsychiatric	Emotional lability Anxiety Confusion Restlessness
Gastrointestinal	Diarrhea Nausea Vomiting
Reproductive	Oligomenorrhea Decreased libido
Cardiovascular	Palpitations Dyspnea Chest pain
Thyroid	Sensation of neck fullness
Dermatologic	Hair loss
Ophthalmologic	Eye irritation Diplopia

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Table 2
Signs of thyrotoxicosis[1,18,21]

Organ System	Sign
Systemic	Diaphoresis Fever Cachexia or emaciated appearance Muscle wasting
Neuropsychiatric	Coma Hyperreflexia Proximal muscle weakness Fine tremor Periodic paralysis Agitation or delirium Convulsions
Gastrointestinal	Abdominal tenderness Hyperactive bowel sounds Jaundice
Reproductive	Gynecomastia/breast enlargement
Cardiovascular	Sinus tachycardia Atrial fibrillation or other tachydysrhythmia Hyperdynamic precordium Congestive heart failure (generally high-output heart failure)
Thyroid	Gross anterior neck enlargement Anterior neck tenderness Audible bruit
Dermatologic	Spider angiomas Palmar erythema
Ophthalmologic	Exophthalmos Ophthalmoplegia Conjunctival injection

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is a biochemical diagnosis based on the presence of a low or undetectable TSH. Further testing will show normal T4 and T3 levels. The patient should lack typical examination and historical features of overt thyrotoxicosis and thyroid storm.[35–37] As subclinical hyperthyroidism can resolve on its own, repeat TSH, T4, and T3 levels should be obtained 3 to 6 months later, before confirming the diagnosis.[37]

Thyrotoxicosis

Thyrotoxicosis, as opposed to subclinical hyperthyroidism, is associated with the pattern of low TSH and *elevated* T3 and T4.[18] T3 and T4 both are largely bound in serum with 0.35% and 0.025% freely circulating, respectively.[18] Thyroid binding globulin is the most noteworthy with regards to binding of T3 and T4.[18] It is recommended to obtain free T3 and T4 levels, whenever able, during the evaluation of thyrotoxicosis. In patients with thyrotoxicosis, it is expected to have elevated total and free T3 from both increased production and increased peripheral conversions.[3,18] Elevated T4 is present in 95% of patients with thyrotoxicosis; however, 5% of patients in North America will present with an elevated T3 and normal T4, termed "T3 Toxicosis."[3,18,28,29]

Other common laboratory abnormalities in thyrotoxicosis include elevated alkaline phosphatase and liver enzymes, leukocytosis, reduced renal function, and hypercalcemia.[3,18,28,29] Patients may also have hyperglycemia secondary to

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catecholamine-induced inhibition of insulin release. Although not often explicitly tested for in the ED, patients may display adrenal inefficiency with vasopressor resistant shock, hyperkalemia, and hyponatremia, as thyrotoxicosis leads to both an accelerated production and a degradation of cortisol.[18] An electrocardiogram should be obtained, which may demonstrate a tachydysrhythmia, and if the patient demonstrates altered mental status, computed tomographic (CT) head scan would also be prudent. Finally, although not necessary for diagnosis, patients may ultimately undergo an outpatient or inpatient radionucleotide uptake scan to better identify the underlying cause (**Fig. 5**).

Thyroid Storm

Approximately 1% to 2% of patients with thyrotoxicosis will develop acute multiorgan injury and thyroid storm.[6] Unlike other forms of hyperthyroidism, diagnosis of thyroid storm is based largely on clinical features.[1,6,18,29] Although these patients will also likely have a low TSH and elevated T3/T4 on laboratory evaluation, the clinical features and physiologic derangements distinguish thyroid storm from thyrotoxicosis. Patients with thyroid storm may present with encephalopathy, cardiac involvement (such as tachydysrhythmias, and congestive heart failure), hyperpyrexia, gastrointestinal hyperactivity, or jaundice.[6] Given the multiple nonspecific signs and symptoms, there are several tools that may assist in diagnosis. The 1993 Burch-Wartofsky Diagnostic Criteria include derangements of different organ systems (**Table 3**).[38] Scores $\geq$ 45 are suggestive of thyroid storm; scores of 25 to 44 are suggestive of impending thyroid storm, and scores less than 25 are not consistent with thyroid storm.[38]

Unfortunately, the Burch-Wartofsky Diagnostic Criteria rely on the presence of nonspecific signs and symptoms without thyroid function testing.[6] The Japanese Diagnostic Criteria of Thyroid Storm include laboratory assays as well as clinical signs and symptoms (**Fig. 6**).[6,39,40] At a minimum, a TSH is required before the application of the scoring system.[6] These criteria include 5 organ systems resulting in clinical manifestations, including the central nervous system (CNS), cardiovascular system (tachycardia and/or congestive heart failure), gastrointestinal system, and autonomic

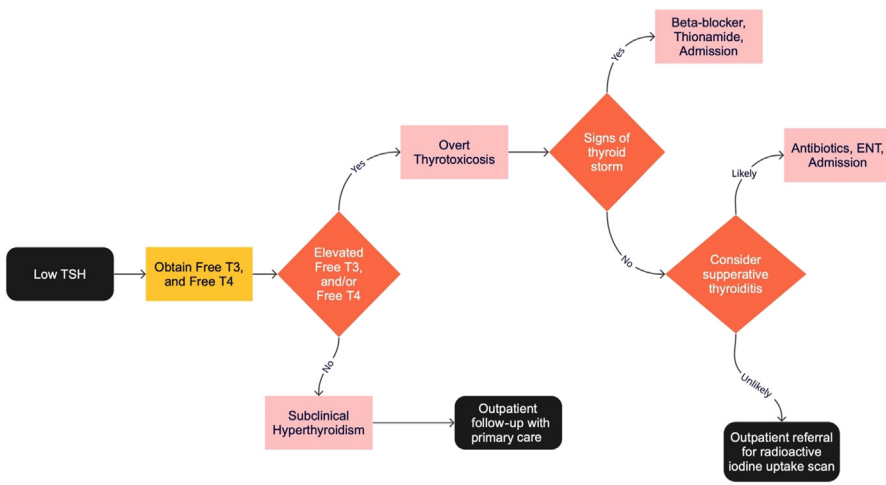

Fig. 5. Workup of hyperthyroidism from the ED. ENT, .

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Table 3
Burch-Wartofsky Diagnostic Criteria for thyroid storm[38]

Diagnostic Criteria	Scoring Points
Thermoregulatory dysfunction	
Temperature (°F)	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥ 104	30
Central nervous system dysfunction	
Absent	0
Mild agitation	10
Moderate (delirium, psychosis, lethargy)	20
Severe (seizure, coma)	30
Gastrointestinal and hepatic dysfunction	
Absent	0
Moderate (nausea/vomiting, diarrhea, abdominal pain)	10
Severe (jaundice)	20
Cardiovascular dysfunction	
Tachycardia (beats/min)	
90–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial fibrillation	
Absent	0
Present	10
Precipitating event	
Absent	0
Present	10

Scores ≥45 are suggestive of thyroid storm.
Scores 25–44 are suggestive of impending thyroid storm.
Scores <25 are unlikely to be consistent with thyroid storm.

systems (Table 4). During these surveys, there were determined to be 2 combinations of clinical manifestations for each survey (TS1 First Combination, TS1 Alternate Combination, TS2 First Combination, TS2 Alternate Combination).[6] Meeting any of the 4 potential combinations is diagnostic of thyroid storm.

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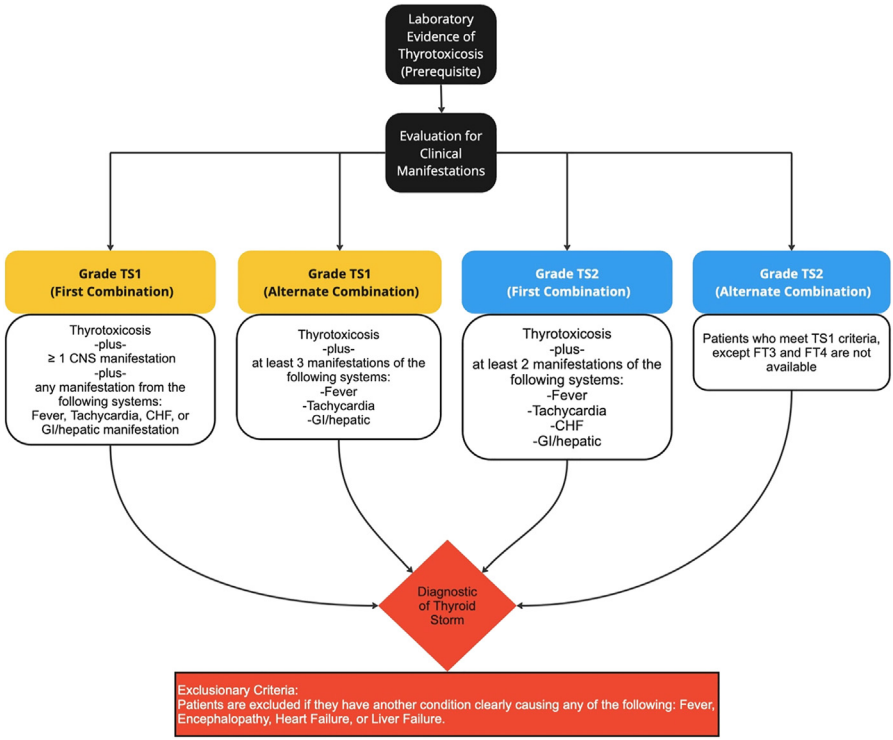
Laboratory Evidence of Thyrotoxicosis (Prerequisite)
Evaluation for Clinical Manifestations
Grade TS1 (First Combination)
Thyrotoxicosis -plus- ≥ 1 CNS manifestation -plus- any manifestation from the following systems: Fever, Tachycardia, CHF, or GI/hepatic manifestation
Grade TS1 (Alternate Combination)
Thyrotoxicosis -plus- at least 3 manifestations of the following systems: -Fever -Tachycardia -GI/hepatic
Grade TS2 (First Combination)
Thyrotoxicosis -plus- at least 2 manifestations of the following systems: -Fever -Tachycardia -CHF -GI/hepatic
Grade TS2 (Alternate Combination)
Patients who meet TS1 criteria, except FT3 and FT4 are not available
Diagnostic of Thyroid Storm
Exclusionary Criteria: Patients are excluded if they have another condition clearly causing any of the following: Fever, Encephalopathy, Heart Failure, or Liver Failure.

Fig. 6. Japanese Diagnostic Criteria for thyroid storm. GI, gastrointestinal.

The application of these tools can aid in the diagnosis and recognition of thyroid storm, but clinicians should not rely on the scores in isolation. Literature suggests the Burch-Wartofsky system is less specific but more sensitive than the Japanese

Table 4
Clinical manifestation included in the Japanese Diagnostic Criteria of thyroid storm[6]

Central nervous system manifestations	• Restlessness • Delirium • Psychosis • Somnolence or lethargy • Coma (≥1 on Japan Coma Scale, or Glasgow Coma Scale ≤14)
Fever	• Temperature ≥38°C
Tachycardia	• Heart rate ≥130 beats per minute (including from arrhythmias, such as atrial fibrillation)
Congestive heart failure (CHF)	• Pulmonary edema • Cardiogenic shock • New York Heart Association class IV CHF • Killip class III or higher CHF • Severe symptoms attributed to CHF
Gastrointestinal and hepatic manifestations	• Nausea • Vomiting • Diarrhea • Bilirubin ≥3 mg/dL

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Criteria.[41] These scores can be used as a framework for diagnosis, and clinicians should consider using both scores in conjunction. Evaluation for an underlying trigger of the patient's thyrotoxicosis is also warranted.

MANAGEMENT

ED management depends on the severity of thyrotoxicosis. The following sections provide an overview of ED management.

Subclinical Hyperthyroid

The natural history of subclinical hyperthyroidism is variable with some patients having spontaneous recovery without intervention.[2,3,39] For these reasons, the treatment of subclinical hyperthyroidism with antithyroid drugs (ATDs) is controversial.[3] US treatment guidelines recommend initiating treatment in patients with a *persistently* low TSH < 0.1 mU/L.[2] Implicit in this recommendation is the need for follow-up and repeat laboratory evaluation before the initiation of ATDs. Therefore, when patients present to the ED with subclinical hyperthyroidism without evidence of thyrotoxicosis, deferring treatment to outpatient providers is reasonable.

Management of Thyrotoxicosis Without Thyroid Storm

Initiation of ATDs from the ED should be approached with caution for those without thyroid storm. The treatment of overt thyrotoxicosis without thyroid storm is directed at the underlying cause.[2] As oral ATDs can take weeks to exert their maximum effects, it is unclear if there is increased utility in initiating treatment with ATDs from the ED. Many patients require definitive treatment with radioactive iodine ablation or thyroidectomy in the outpatient setting.[2] Beta-blockers are recommended for *all* symptomatic thyrotoxic patients by American Thyroid Guidelines, as short-term use has been shown to improve heart rate, dyspnea, and fatigue compared with methimazole (MMI) alone (**Table 5**).[2,42]

Management of Thyroid Storm

Patients with thyroid storm typically have an underlying trigger (see **Box 2**). The underlying source should be identified and managed, concurrent with the diagnosis and treatment of thyroid storm.

Table 5
Beta-blocker dosing for the treatment of thyrotoxicosis without thyroid storm[2]

Medication	Typical Dose	Typical Frequency	Considerations and Rationale
Propranolol	10–40 mg	3–4 times/d	Nonselective ß-blockade Blocks T4 → T3 conversion Preferred in pregnant and nursing mothers Most commonly used
Atenolol	25–100 mg	1–2 times/d	Better compliance Avoid in pregnancy $ß_1$ selective
Metoprolol	25–50 mg	2–3 times/d	Mostly $ß_1$ Once daily dosing is available
Nadolol	40–160 mg	Once per day	Nonselective ß-blockade Least commonly used

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Emergent medical management of thyroid storm consists of order-specific therapies. However, as with all critically ill patients, emergent management first begins with evaluation and the intervention upon the ABCs (airway, breathing, and circulation). Patients first require hemodynamic support, which may include intravenous (IV) fluids owing to dehydration associated with insensible loss, vomiting, and diarrhea. Vasopressors may be required. Broad-spectrum antibiotics should be administered, and blood and urine cultures should be obtained, as an infection is a common precipitant of thyroid storm.[43]

In patients presenting with hyperpyrexia or fever, management with external cooling and acetaminophen is indicated.[2,18,39] Although treatment of hyperpyrexia has not been shown to reduce mortality, it may decrease demand on the CNS and cardiovascular system.[39] Treatment of fever with nonsteroidal anti-inflammatories, and notably salicylates, increases serum levels of free thyroid hormone and is not recommended.[39]

The first medication to administer is typically some form of a ß-antagonist.[2,18,39] Historically, propranolol is the preferred ß-blockade pharmacotherapy given its nonselective nature.[2] Propranolol decreases the peripheral conversion of T4 to T3, although the exact mechanism remains speculative.[2] Importantly, caution is recommended with the administration of ß-blockade in patients with thyroid storm, as multifactorial shock may be present. Tachycardia may be compensatory for the underlying condition and be exaggerated by the hyperadrenergic state, rather than due solely to thyroid storm. Underlying cardiac dysfunction in thyroid storm is estimated to affect 6% to 19% of cases, with mortalities approaching 30%.[44,45] In patients given propranolol, cardiogenic shock has been reported, particularly in patients with reduced left ventricular ejection fraction.[44] Therefore, it is recommended performing a point-of-care transthoracic echocardiogram to evaluate cardiac function before the administration of a ß-blockade agent if possible. In cases with depressed left ventricular contractility, ß-blockade should be avoided.

Patients with hyperdynamic cardiac function can receive a ß-blocking agent. In these cases, use of an ultrashort-acting agent, such as esmolol (half-life 9 minutes), is best supported by the current evidence, as propranolol is associated with higher mortalities compared with short-acting agents, such as esmolol.[39,44,45] Last, in cases whereby propranolol or esmolol are not available and ß-blockade is deemed appropriate, alternate options for ß-blockade include atenolol and metoprolol (**Table 6**).[2,39,44]

Table 6
Beta-blocker dosing for the treatment of thyroid storm[2,18,39,44]

Medication	Typical Dose	Considerations and Rationale
Propranolol	60–80 mg every 4 h Or 80–120 mg every 6 h	Nonselective ß-blockade Blocks T4 → T3 conversion Preferred in pregnant and nursing mothers Most commonly used
Atenolol	50–200 mg daily	Better compliance Avoid in pregnancy $ß_1$ selective
Metoprolol	25–50 mg	Mostly $ß_1$ Once daily dosing is available
Esmolol	500 μg/kg load, then 50–100 μg/kg/min	$ß_1$ selective Very short half-life ($t_{1/2}$ = 9 min)

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Administration of an ATD is also necessary in thyroid storm. The primary class of antithyroid pharmacologic agents is thionamides, including propylthiouracil (PTU) and MMI in the United States.[2,3,5,18,21,39,40,43,46] Carbimazole, a precursor agent of MMI, is available in Europe and Asia.[3] Thionamides decrease thyroid hormone production by interfering with thyroid peroxidase–catalyzed coupling, exerting their effect over the course of several weeks.[3,18,47] PTU is the preferred agent given its long track record, as well as a suspected decrease in the peripheral conversion of T4 to T3.[2,39,44] In cases whereby PTU is not available, or the patient has a contraindication, MMI may be administered (**Table 7**). In cases whereby carbimazole is administered, 10 mg of carbimazole is metabolized to 6 mg of MMI.[2]

Because of the risk of adrenal insufficiency, systemic steroids are recommended.[2,5,18,21,28,39] Hydrocortisone 300 mg IV load is recommended, although methylprednisolone or dexamethasone can be used (**Table 8**).

Iodine is indicated to inhibit the release of stored thyroid hormone via the Wolff-Chaikoff effect (**Table 9**).[39] Iodine administration should be delayed *at least* 1 hour after the administration of thionamides owing to the potential for an erroneous massive release of thyroid hormone in the setting of an iodine load (Jod-Basedow phenomenon).[2,18,28] The minimum effective dose of iodine is estimated to be 5 to 10 mg/d,

Table 7
Thionamide dosing for the treatment of thyroid storm[2,18]

Medication	Typical Dose	Considerations and Rationale
Propylthiouracil	500–1000 mg load, then 250 mg every 4 h	Decreases new thyroid hormone production Blocks T4 → T3 conversion IV route available
Methimazole	20–25 mg every 6 hours or 60–80 mg per day	Decreases new thyroid hormone

Table 8
Steroid dosing for the treatment of thyroid storm[2]

Medication	Typical Dose	Considerations and Rationale
Hydrocortisone	300 mg load Then 100 mg every 8 h	Improve vasomotor stability Blocks T4 → T3 conversion

Table 9
Inorganic iodine dosing for the treatment of thyroid storm[2,18,39]

Medication	Typical Dose	Considerations and Rationale
Potassium iodide	5 drops orally every 6 h	Must wait ≥1 h after thionamide administration
Lugol solution	4–8 drops orally every 6–8 h	Must wait ≥1 h after thionamide administration
Sodium ipodate	1–3 g orally daily	Must wait ≥1 h after thionamide administration
Iopanoic acid	1 g orally every 8 h for 24 h, then 500 mg every 12 h	Must wait ≥1 h after thionamide administration

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although owing to alterations in uptake in the setting of this acute critical illness, the recommended dosing is 200 mg/d.[39]

In patients who cannot receive either PTU, MMI, or iodine, lithium carbonate can decrease the release of stored thyroid hormone.[2,18,39] If lithium is administered, serum levels must be monitored to avoid toxicity (**Table 10**).[2,18,39]

Following the use of the above therapies, alternative therapies or adjunctive therapies may be administered in cases of severe or refractory critically ill patients. In patients who fail to improve in 24 to 48 hours, therapeutic plasma exchange may be helpful, particularly in cases of encephalopathy and liver failure.[39] In patients who fail to improve or continue to deteriorate despite maximal conventional therapies, the use of extracorporeal cardiovascular support may be used to mitigate irreversible cardiovascular effects.[39] One study demonstrates a 40% decrease in mortality with the use of mechanical support in patients with cardiogenic shock.[44] Finally, a useful adjunctive therapy for patients in thyroid storm includes binding resins, such as cholestyramine. Cholestyramine binds iodothyronine, attenuating enterohepatic circulation and promoting the excretion of thyroid hormone (**Table 11**).[39]

Table 10
Lithium dosing for the treatment of thyroid storm[18]

Medication	Typical Dose	Considerations and Rationale
Lithium carbonate	300 mg every 8 h	Stops release of preformed hormone May inhibit new hormone synthesis Monitor to achieve a serum lithium level of 0.6–1 meq/L

Table 11
Cholestyramine dosing for the treatment of thyroid storm[39,43]

Medication	Typical Dose	Considerations and Rationale
Cholestyramine	1–4 mg bid	Attenuates enterohepatic circulation of iodothyronine

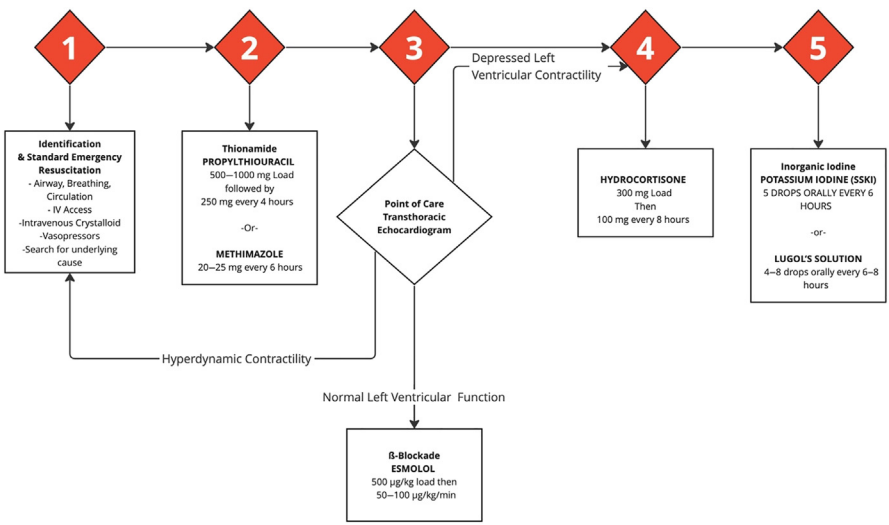

Fig. 7. Management of thyroid storm in the ED. SSKI, potassium iodide.

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Of note, this approach is a general framework, but resuscitation is emergently needed in patients with thyroid storm (**Fig. 7**). Patients with thyroid storm may rapidly decompensate and require adjunctive supportive measures and, therefore, should be admitted to the intensive care unit.[39]

SUMMARY

Hyperthyroidism is a spectrum of diseases encompassing subclinical hyperthyroidism, overt thyrotoxicosis, and thyroid storm. There are several causes for the development of hyperthyroidism, the most common of which is GD. The treatment of thyrotoxicosis is generally tailored to the individual patient's etiology. The diagnosis of thyroid storm is heavily dependent on the recognition of clinical features. Patients with thyroid storm are critically ill and require emergent resuscitation and treatment while being evaluated for the underlying cause. Management focuses on hemodynamic stabilization; administration of thionamides, steroids, and iodine; and treatment of any underlying stressor.

CLINICS CARE POINTS

- Patients with subclinical hyperthyroidism generally need follow-up testing for formal diagnosis.
- Elderly patients may present with apathetic thyrotoxicosis and paradoxically diminished mentation.
- Patients with suppurative thyroiditis have high mortality and are easily confused for patients with thyroiditis.
- The diagnosis of thyroid storm is based heavily on clinical assessment and evaluation for end-organ injury. Clinical support tools include the Burch-Wartofsky Diagnostic Criteria and Japanese Diagnostic Criteria.
- Patients with thyroid storm have a predilection for the development of cardiogenic shock, particularly if they have diminished left ventricular ejection fraction.
- Treatment of thyroid storm includes diagnosing and managing the underlying trigger (eg, antibiotics for infection); administration of thionamides, steroids, and iodine; and treatment of any underlying stressor.
- Fever should be treated with acetaminophen (paracetamol). Salicylates and nonsteroidal anti-inflammatory drugs should be avoided.

DISCLOSURES

There are no conflicts to disclose.

DISCLAIMER

The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the US Army Medical Department, the US Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, and Department of Defense, or the US Government.

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